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The association of HIV-1 Gag-specific IgG antibodies with natural control of HIV-1 infection in individuals not carrying HLA-B*57:01 is only observed in viremic controllers

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Abstract

To expand upon our previous observation that HIV-1 Gag-specific IgG antibodies were highest in HIV controllers not carrying HLA-B*57:01, we analysed these antibodies in a larger cohort of viremic controllers (VCs) or elite controllers (ECs) considering carriage of 'protective' HLA-B alleles. HIV-1 p24-specific IgG1 and IgG2 antibodies were higher only in HLA-B*57:01^{-} VCs but there were no differences in ECs. Associations of HIV-1 gp140-specific IgG antibodies with HLA-B*57:01 carriage were inconsistent amongst VCs and ECs.

Keywords

HIV-1 p24-specific IgG antibodies; HIV-1 gp140-specific IgG antibodies; protective HLA-B alleles; viremic controllers; elite controllers

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Contributions

The manuscript was written by M.A.F., M.C.T and S.F. Laboratory work was performed by M.C.T., M.A.M., L.S., S.L., S.F. and D.B.A.T. Data analyses were performed by M.C.T. Patient plasma samples were provided by S.G.D and J.N.M. All authors reviewed and provided comment on the manuscript.

Defining immune responses that naturally control HIV-1 infection will enlighten therapeutic HIV-1 vaccine design. It is well-established that $CD8^+$ T cell responses against peptides of HIV-1 capsid proteins encoded by *gag* (Gag proteins) and carriage of 'protective' alleles of genes for human leucocyte antigen (HLA)-B molecules, which present peptides of HIV-1 Gag proteins to $CD8^+$ T cells, correlate with immune control of HIV-1 infection [1–3]. In individuals of European descent, the most 'protective' allele of HLA-B is HLA-B*57:01 [3], which encodes HLA molecules that bind fewer self-peptides and exhibit greater cross-reactive binding of viral peptides than other HLA-B alleles, contributing to exceptional long-term control of HIV-1 replication in carriers [4]. However, approximately 30–40% of individuals who naturally control HIV-1 infection (HIV controllers) do not possess a 'protective' HLA-B allele [1, 2], suggesting that immune responses other than those mediated by $CD8^+$ T cells contribute to immune control of HIV-1 infection. Recently, Koofhethile et al. [5] demonstrated that viremic controllers (VCs) not carrying 'protective' alleles of HLA-B genes control HIV-1 infection more robustly than carriers, and that $CD8^+$ T cells do not mediate this effect. In addition, Freund et al. [6] demonstrated that HIV-1 Env-specific antibodies with broad neutralising activity might have contributed to long-term control of HIV-1 infection in an elite controller (EC) who carried the 'protective' HLA-B alleles HLA-B*57:01 and HLA-B*27:05. However, the findings of previous studies on the role of antibodies in the natural control of HIV-1 infection have been inconclusive [2, 7–11].

We have previously provided evidence that HIV-1 Gag-specific IgG antibodies might contribute to control of HIV-1 infection [12–15], including in HIV controllers not carrying HLA-B*57:01 [13], and proposed that these antibodies mediate HIV-1 Gag-specific pDC-reactive opsonophagocytic antibody (PROAb) responses [14]. Importantly, in analysing the relationship between HIV-1 Gag-specific IgG antibodies and 'protective' HLA-B alleles in our previous study [13], we did not differentiate between VCs and ECs. We have therefore undertaken this analysis for the patients reported in Tjiam et al. [14]. As both IgG1 and IgG2 antibodies contribute to opsonophagocytic antibody responses that activate dendritic cells via FcγRIIa [16], we examined HIV-1 p24-specific IgG1 and IgG2 antibody levels and HIV-1 p24-specific PROAb responses in the previously reported VCs (n=29) and ECs (n=30) [14] stratifying them into subgroups based on carriage, or not, of HLA-B*57:01 or other 'protective' HLA-B alleles (HLA-B*14:02, 27:05, 52:01, 58:01 and 81:01) defined in European and African patients [3, 5]. Non-controllers (NCs; n=30) were included for comparison.

As shown in Figure 1, HIV-1 p24-specific IgG1 and IgG2 antibodies were higher in VCs than NCs, except for VCs carrying HLA-B*57:01 (Figures 1A, B). HIV-1 p24-specific PROAb responses were also higher in VCs than NCs but a relationship with 'protective' HLA-B alleles was not apparent (Figure 1C). In contrast, ECs exhibited essentially no differences in HIV-1 p24-specific IgG antibodies when compared with NCs (Figures 1D-F). We also examined the relationship of HIV-1 gp140-specific IgG1 and IgG2 antibody levels, demonstrated in these patients [14], with 'protective' HLA-B alleles (Figures 1G-J). HIV-1 gp140-specific IgG2 antibodies exhibited a relationship to HLA-B*57:01 that was similar to HIV-1 p24-specific IgG2 antibodies but in ECs rather than VCs (Figure 1J). In VCs, HIV-1 gp140-specific IgG1 antibodies were higher in patients carrying HLA-B*57:01 (Figure 1G).

These findings expand upon our previous findings [13] by demonstrating that the association between HIV-1 p24-specific IgG antibodies and natural control of HIV-1 infection in individuals not carrying HLA-B*57:01 is only observed in VCs. This observation was made for HIV-1 p24-specific IgG1 and IgG2 antibodies but not for PROAb responses, possibly because they are detected by a functional antibody assay that may be affected by factors other than binding of antibodies to antigens in an enzyme immunoassay. Furthermore, our findings provide more evidence that IgG2 antibodies to HIV-1 Env antigens are associated with control of HIV-1 infection [10, 17], but only in ECs not carrying HLA-B*57:01. We suggest that HIV-1 p24-specific IgG1 and IgG2 antibodies, possibly including PROAb responses, might contribute to non-$CD8^+$ T cell-mediated control of HIV-1 infection in patients with low-level HIV-1 replication [5] and that this requires further investigation. We also suggest that these investigations should consider the possibility that HIV-1 Gag-specific IgG antibodies mediate an antibody response against HIV-1 capsids extracellularly via PROAb responses mediated through FcγRIIa [14] and/or intracellularly via the neonatal Fc receptor and the cytosolic Fc receptor TRIM21/Ro52 [18, 19]. The former type of antibody response has been associated with immune control of non-enveloped RNA viruses [20–22], where antibody-mediated opsonisation of virions leads to their phagocytosis by pDCs and interferon-α production through viral RNA binding to TLR7, and also with control of enveloped influenza viruses by a similar mechanism in mouse models of influenza virus disease [23]. We also demonstrated that carriage of HLA-B*57:01 was associated with HIV-1 gp140-specific antibody levels in HIV controllers but in contrast to HIV-1 p24-specific antibodies, the patterns of association were inconsistent. Thus, HIV-1 gp140-specific IgG1 antibody levels were higher in VCs carrying HLA-B*57:01 while IgG2 antibody levels were higher in ECs not carrying HLA-B*57:01. While it was notable that lack of HLA-B*57:01 carriage was associated with higher HIV-1 gp140-specific IgG2 antibodies in ECs as well as higher HIV-1 p24-specific IgG1 and IgG2 antibodies in VCs, it was not possible to determine if gp140-specific IgG2 antibodies in ECs correlated negatively with HIV viral load, as was shown for HIV-1 p24 IgG antibodies in viremic patients [14].

In conclusion, our findings highlight the importance of examining patients with active HIV-1 replication, and considering the exceptional effects of HLA-B*57:01 on control of HIV-1 infection, when investigating the role of HIV-1 Gag-specific IgG antibodies in controlling HIV-1 infection.

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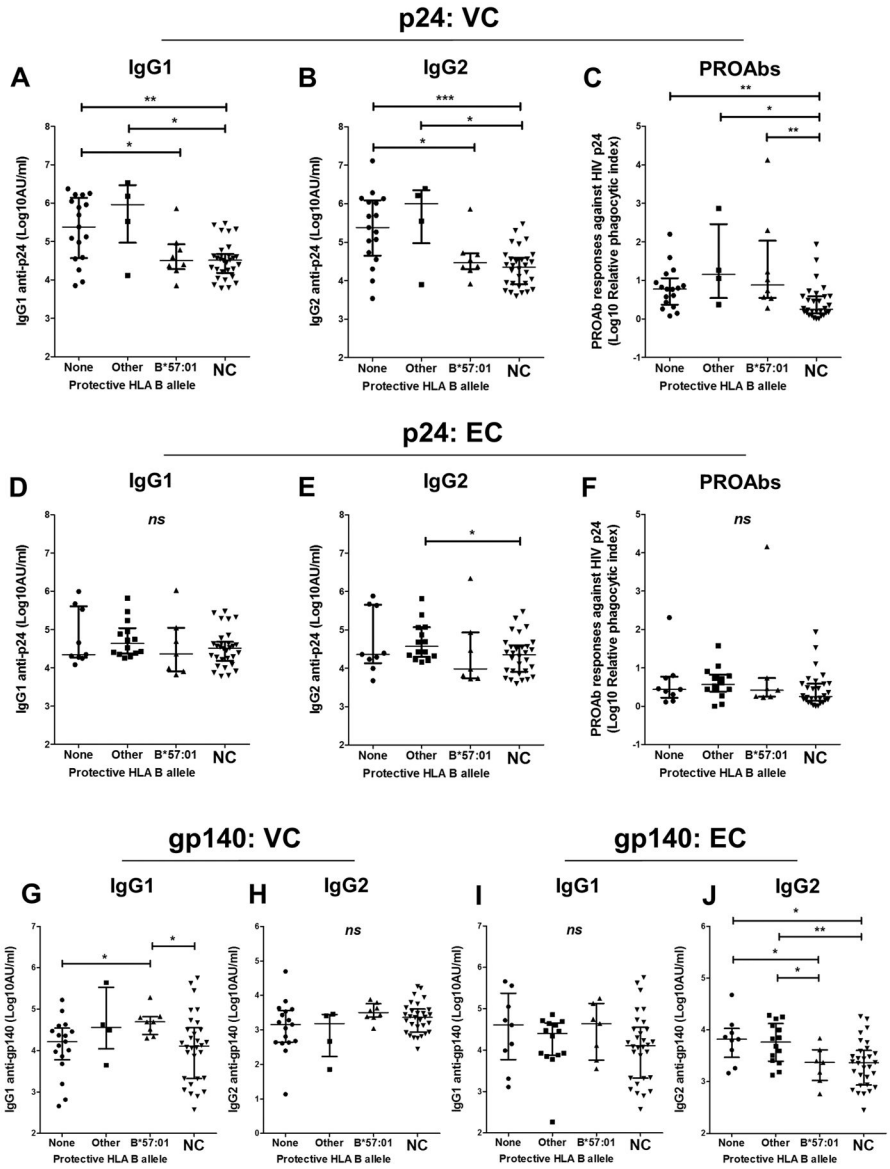

Figure 1.

Based on plasma HIV-1 RNA levels, antiretroviral-naïve HIV-1-infected individuals were classified as either elite controllers (<75 copies/ml), viremic controllers (75–2000 copies/ml) or non-controllers (>10,000 copies/ml). Viremic and elite controllers were subgrouped based on possession of either HLA-B*57:01, other 'protective' HLA-B alleles (HLA-B*14:02, B*27:05, B*52:01, B*58:01, B*81:01) or no 'protective' HLA-B alleles. HIV non-controllers (NC) were included for comparison. Within viremic controllers, differences in IgG antibody responses against HIV-1 p24 (A–C) and HIV-1 gp140 (G, H) between subgroups are shown. Within elite controllers, differences in IgG antibody responses against HIV-1 p24 (D–F) and HIV-1 gp140 (I, J) between subgroups are shown. Differences between subgroups were compared using Mann-Whitney tests (* = $p \leq 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, ns = $p > 0.05$).